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Advances in Insulin Therapy Using Non-Insulin and Insulin Injectables

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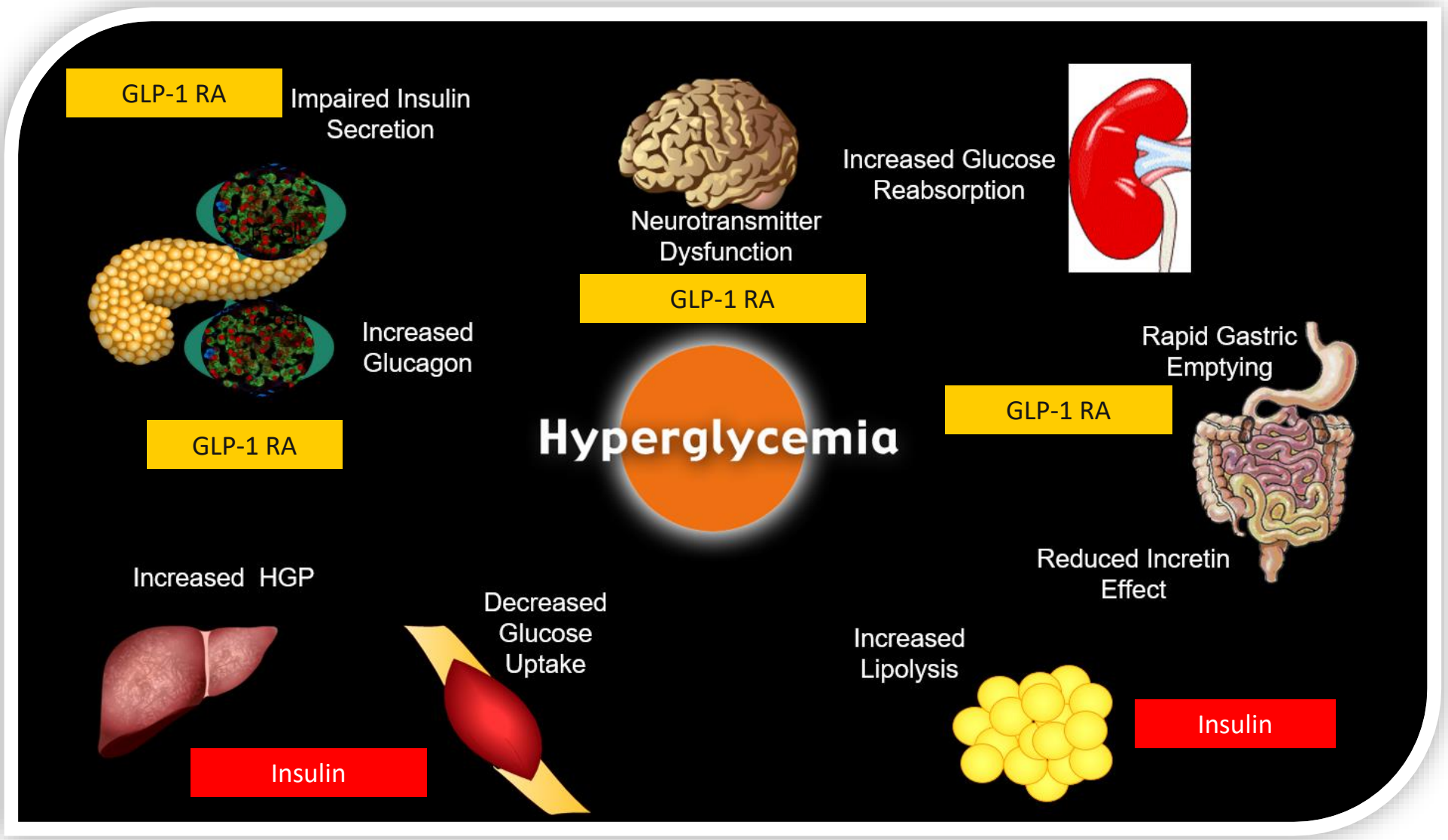
Dualities

Research: Medtronic Diabetes, Insulet, Beta Bionics

Consulting: Abbott Diabetes Care, Roche, Bigfoot, GWave

Multiple Metabolic Abnormalities Contribute to Hyperglycemia in T2DM: GLP1 RA and Insulin Rx



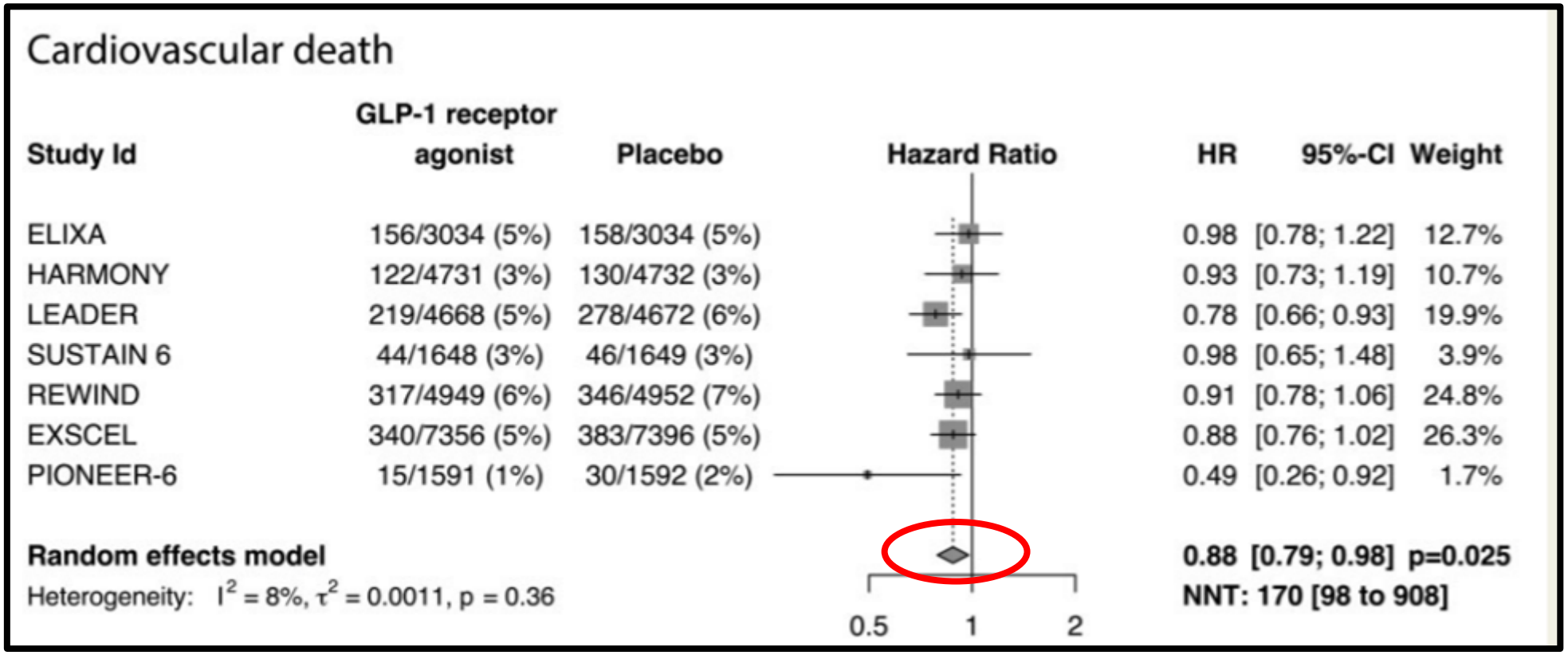
Adapted from DeFronzo, *Diabetes*. 2009;58:773-795

What is the evidence?

GLP1 RA Updates

- GLP-1 RAs are now the first-line injectable therapy for type 2 diabetes
- GLP-1 RAs (and SGLT-2i's) for CV or renal benefit for people with type 2 diabetes should now be *considered independently* of baseline or target A1c

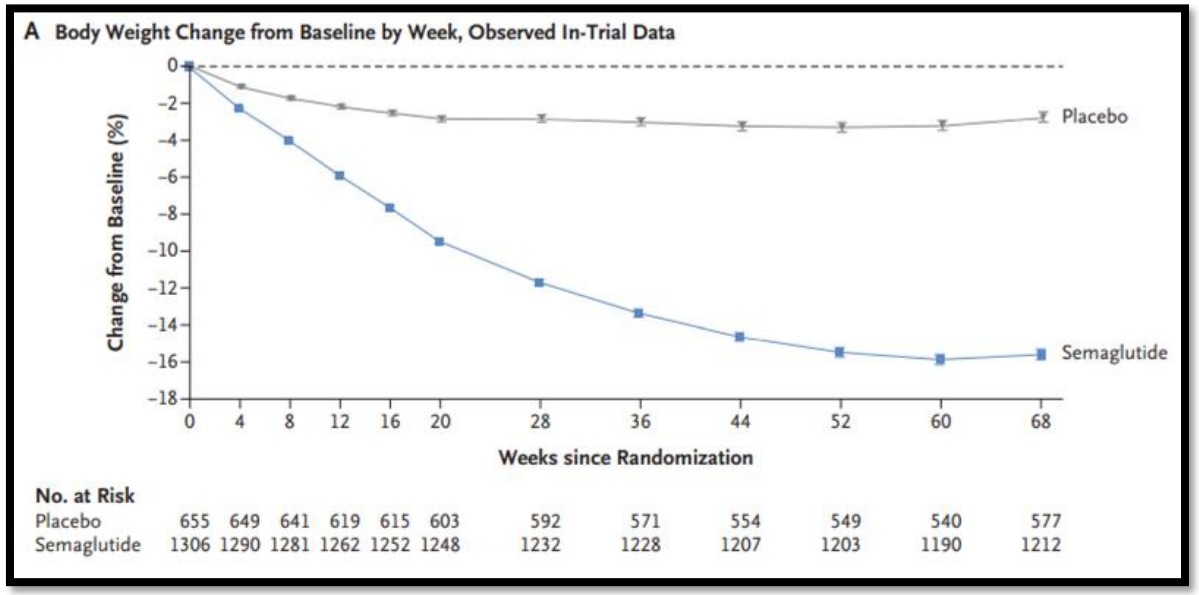
The Effect of GLP1-RAs on CV Death

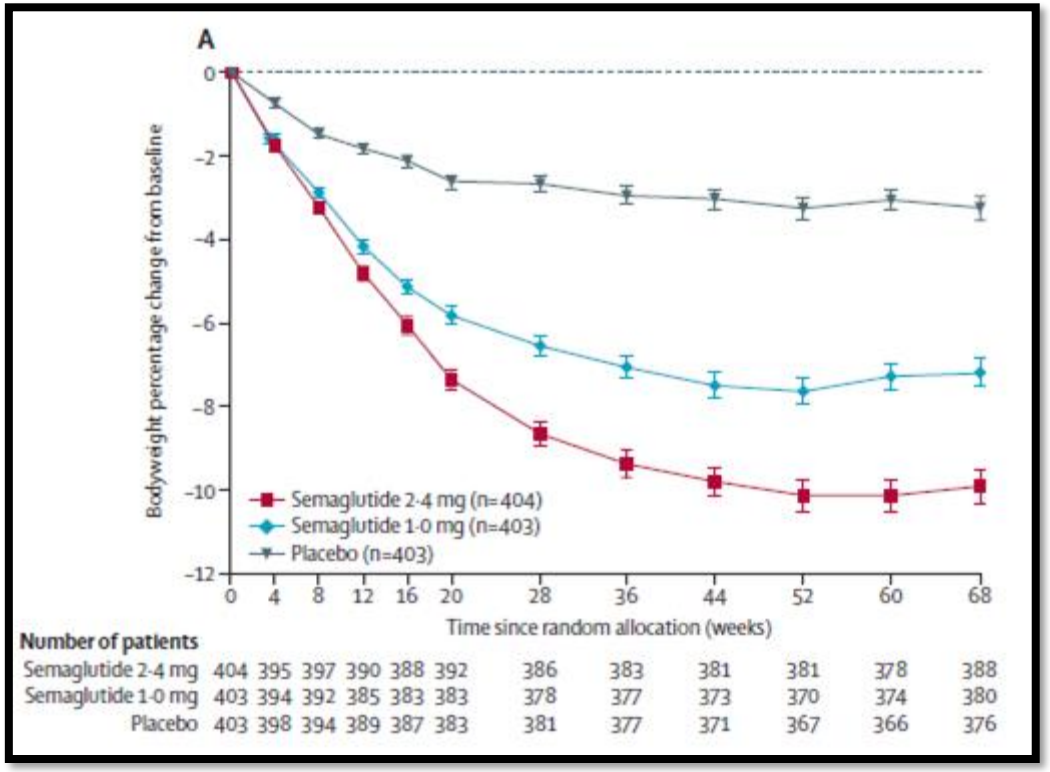


GLP-1RAs: No effect on HF

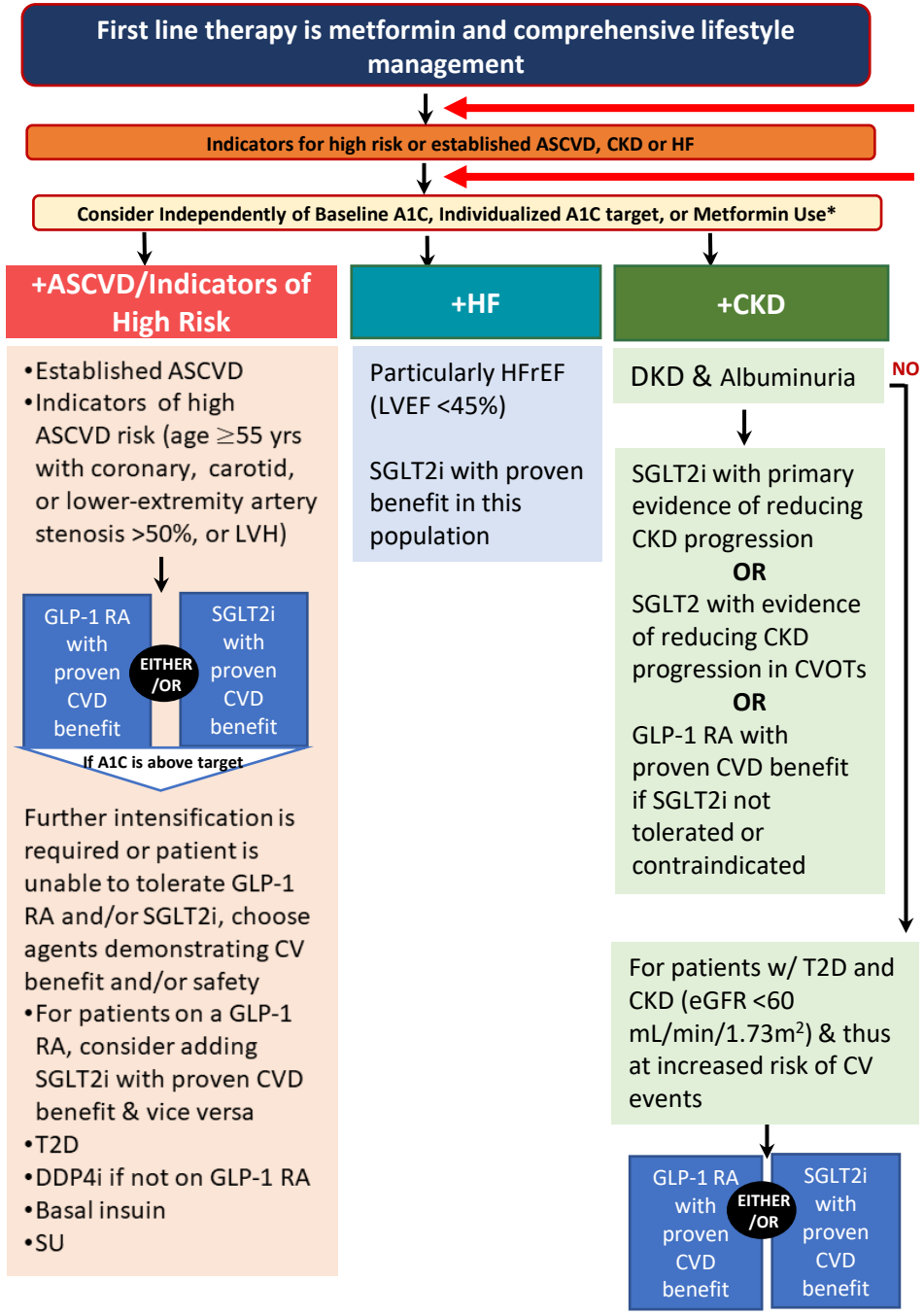
Marsico P et al, *European Heart Journal* 2020; 41:3346–3358

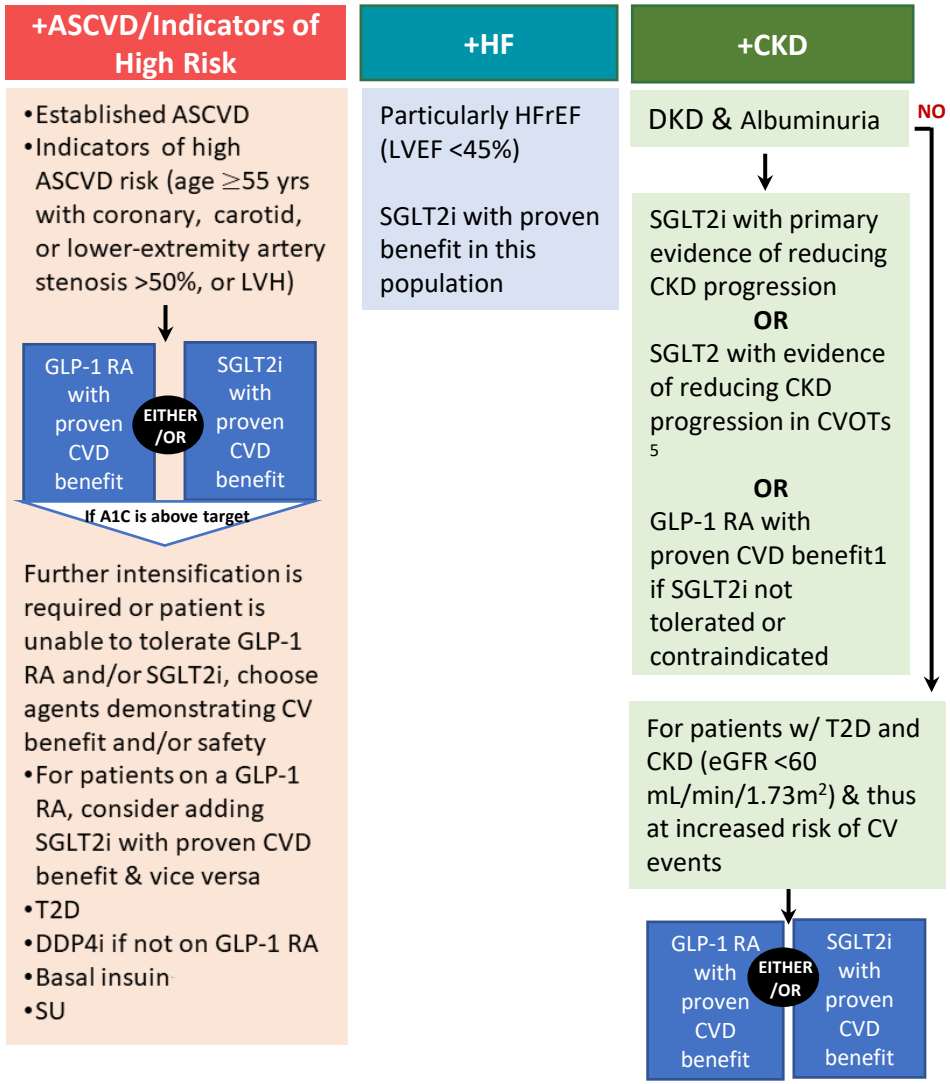
GLP1 RAs Continue to Be Developed for Weight Loss, With or Without Diabetes





N Engl J Med 2021;384:989-1002
Lancet 2021;397:971-984





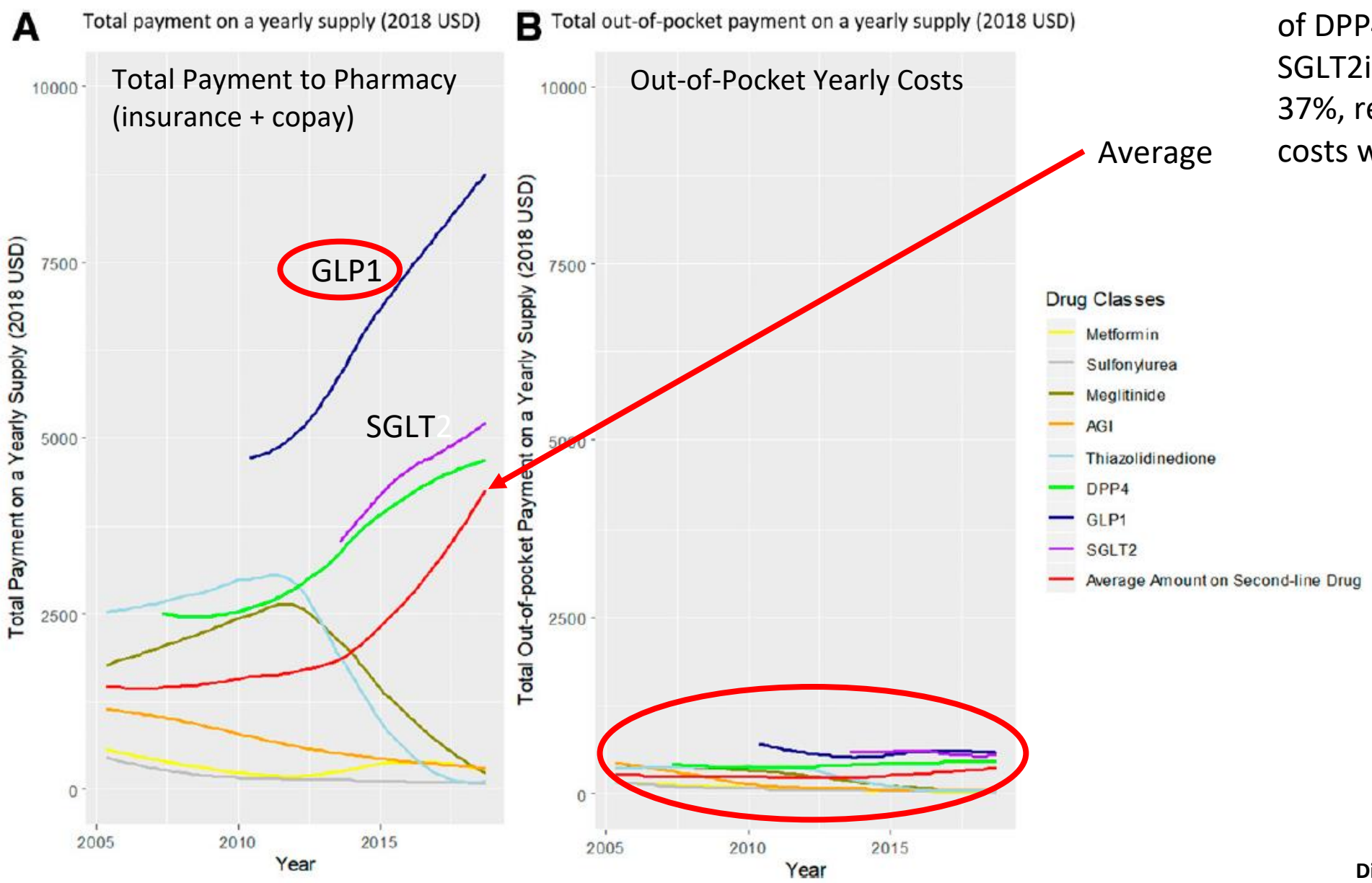
ASCVD=atherosclerotic cardiovascular disease, CKD=chronic kidney disease, GLP-1RA=glucagon-like peptide-1 receptor agonist, SGLT28i=sodium-glucose cotransporter-2 inhibitor, AGI=alpha-glucosidase inhibitor, SFU=sulfonylurea, TZD=thiazolidinedione

American Diabetes Association Diabetes Care 2021;44:S111-S124

Limitations of GLP1 RA vs. Insulin Rx

- GLP1 RA
  - GI side effects*
  - Pancreatitis contraindication
  - Injection
  - Cost
- Insulin
  - Hypoglycemia*
  - Weight gain
  - Need for frequent glucose monitoring (CGM ideal for prandial insulin)
  - Cost

Another Fact to Consider: The Cost of GLP1-RAs and other Non-Insulin Agents

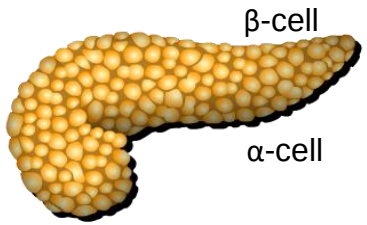


Increase in costs from the launch of DPP4i's, GLP1RAs, and SGLT2i's were 88%, 78%, and 37%, respectively, while the OOP costs were relatively stable.

Diabetes Care 2021 Apr; 44(4): 925-934.

GLP-1 RAs: Why They Make So Much Sense to Use With Basal Insulin

ß and α cell dysfunction



GLP1 RAs: improves ß and α cell function, delays gastric emptying, suppresses appetite

Fixed-Ratio GLP1-insulin
IGlar-Lixi
IDeg-Lira

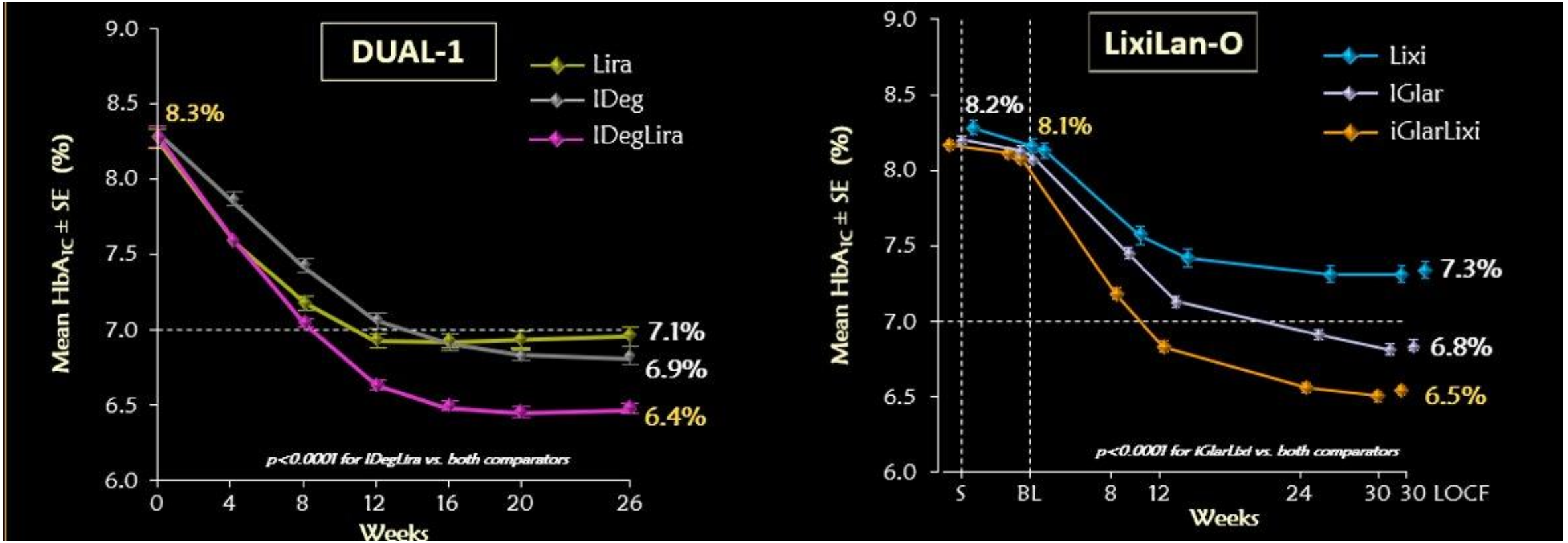
Increased HGP

Basal insulin: targets the Liver to suppress HGP by Reducing gluconeogenesis and glycogenolysis

Complementary Actions

Advances in Therapy 2019; 36(2): 265-277.

Registration Studies: Fixed-Ratio Basal Insulin-GLP1RA Combo



Gough SC, et al. Lancet Diabetes Endocrinol 2014; Rosenstock J, et al. Diabetes Care 2016

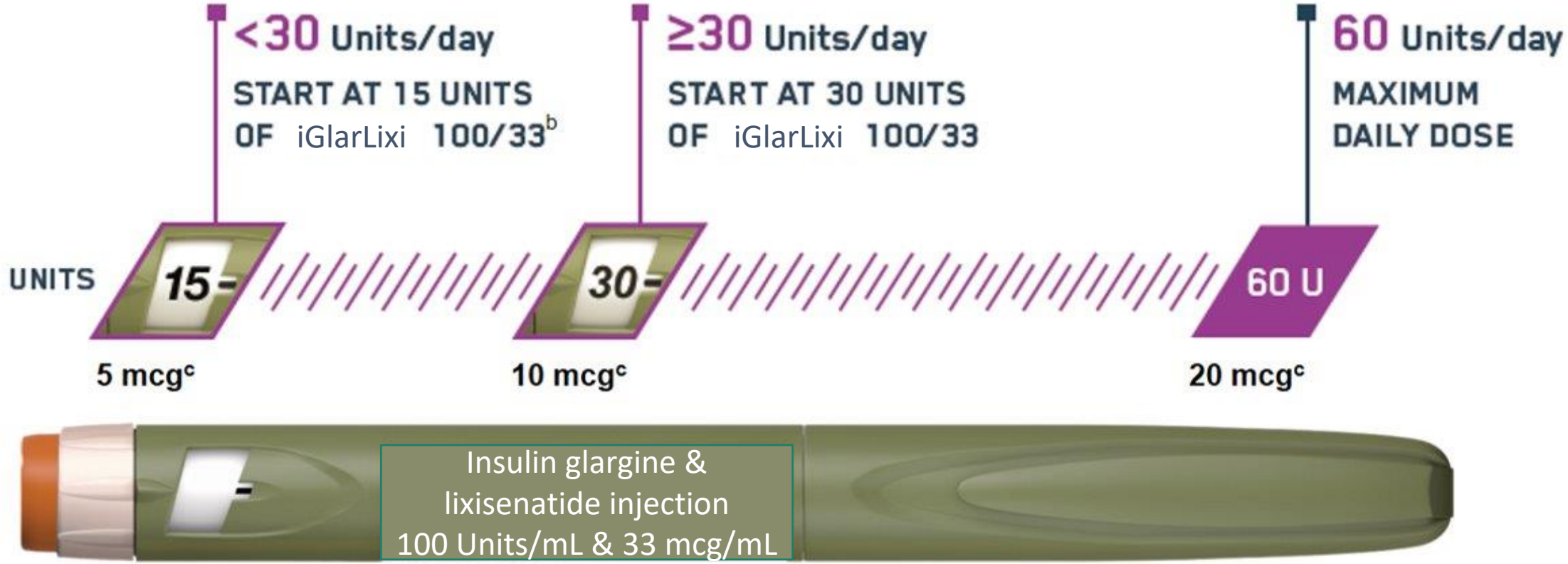
IDegLira 100/3.6

100 units = 100 units degludec, 3.6 mg liraglutide

1. Recommended starting dose (receiving basal insulin): 16 units (16 units degludec, 0.6 mg of liraglutide)
2. Recommendation is to titrate up or down by 2 units every 3 to 4 days based on SMBG
3. Pen delivers 10 units (10 units degludec, 0.4 mg liraglutide) to 50 units (50 units degludec, 1.8 mg liraglutide)

IGlarLixi 100/33

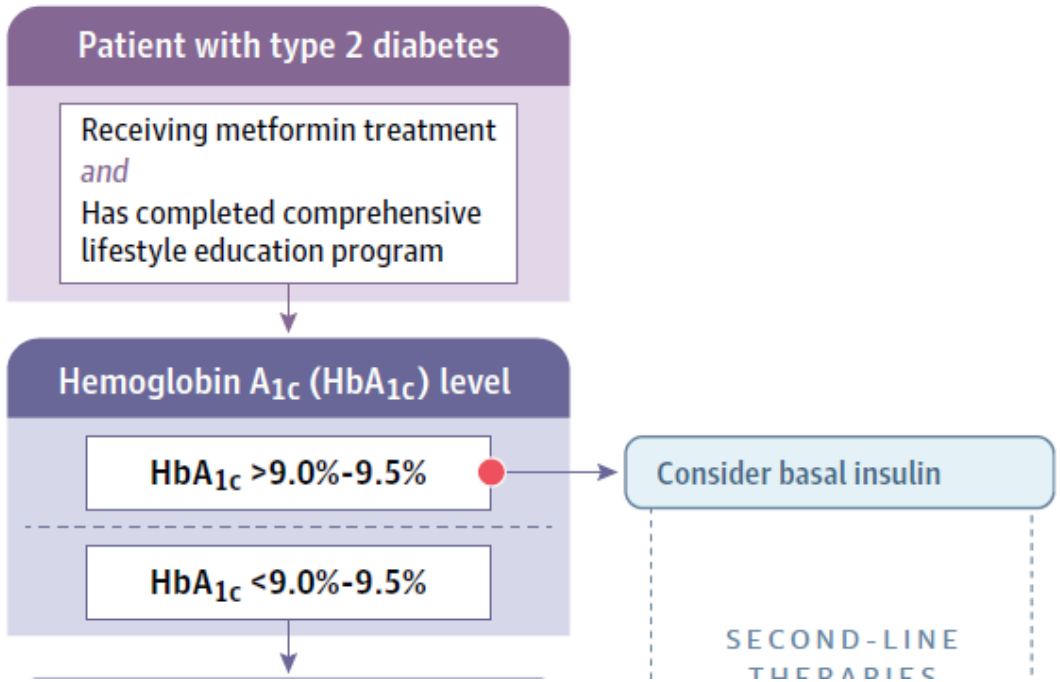
For patients uncontrolled on a basal insulin dose of[a]:



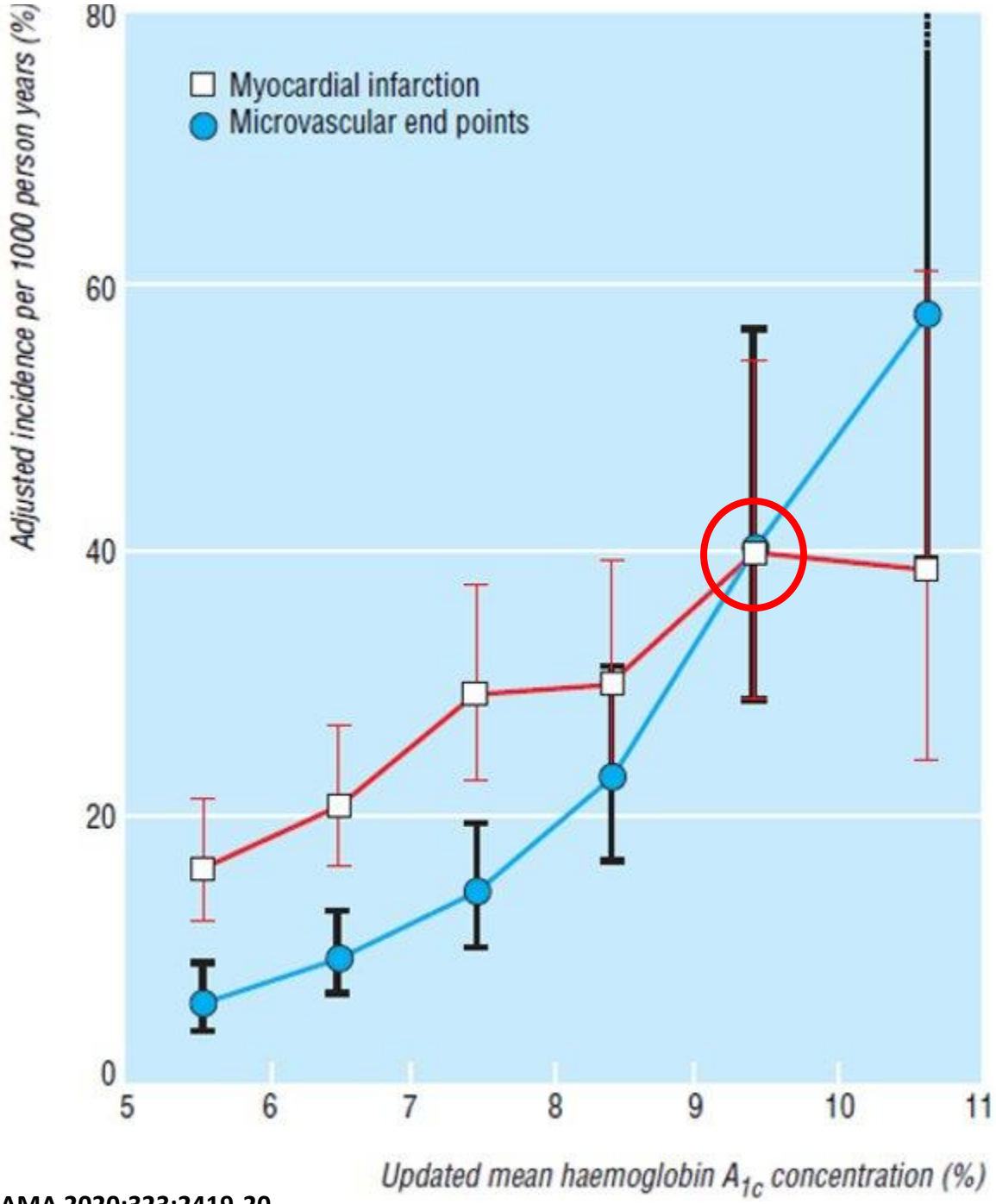
Talking to Patients About Starting a GLP1RA

- Discuss advantages – great efficacy, weight loss, blood pressure reduction
- Discuss CVD and probable renal benefits
- Discuss adverse events
  - Nausea, other GI adverse events; generally, resolves over time; consider in the context of satiety

If A1C is > 10% on metformin monotherapy, with or without ASCVD or CKD, the toxicity of the hyperglycemia needs to be treated while awaiting other drugs to take effect (not to mention the hassle with the PA, patients finding out they can't afford the med when they get to the pharmacy, etc.)



Why not just start basal insulin (or basal insulin with a GLP1 RA) while on the steep part of the curve (and avoid "clinical inertia")?



JAMA 2020;323:2419-20

Advances: Basal Insulin

- The primary role of endogenous basal insulin secretion is to fine tune lipolysis and hepatic glucose production in the fasting state, especially overnight, while maintaining sufficient glucose for brain function
- Goal of exogenous insulin with severe insulin deficiency
  - Attempts to recreate constant, low levels of insulin overnight and between meals which with the correct dose will maintain euglycemia for 24 hours in the fasting state

What is the Correct Dose of Basal Insulin?

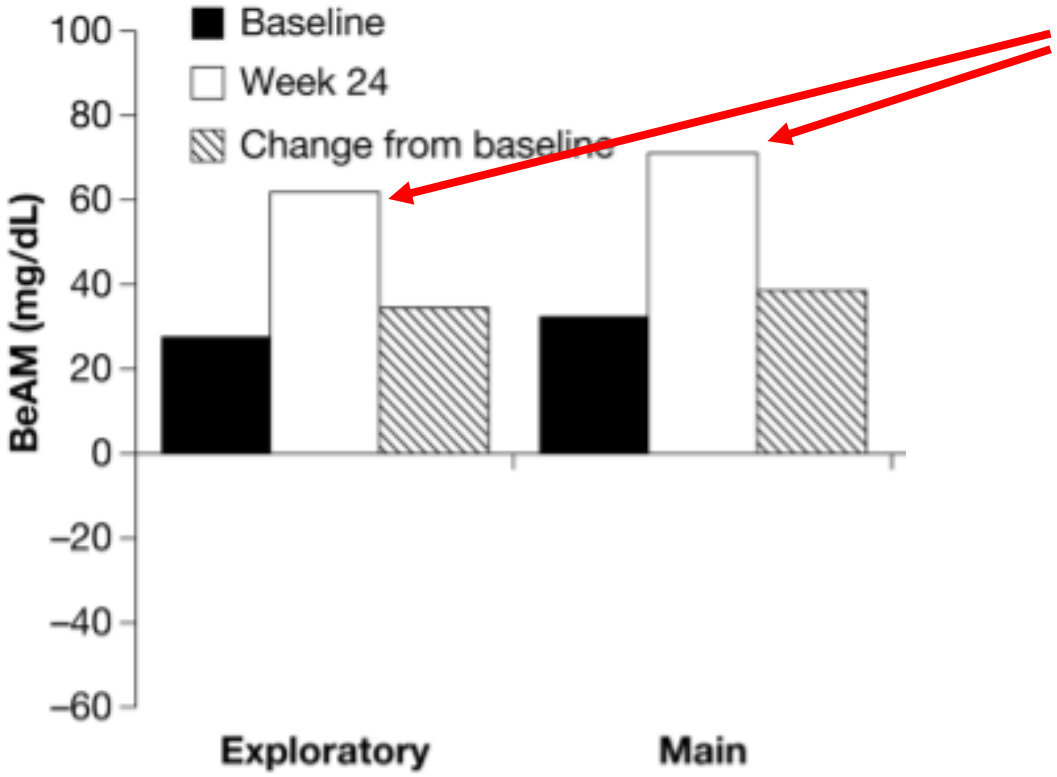
- Traditional Teaching: MDI: 50% basal/50% prandial (T1D, isocaloric diet)
- But what about T2D?

How to Dose Basal Insulin?

- BeAM factor = bedtime glucose – AM glucose
- A + BeAM factor: bedtime glucose is higher than AM glucose
  - For example, mean HS BG = 200, mean FBG = 100, BeAM = 100
- A – BeAM factor: bedtime glucose is lower than AM glucose
  - For example, mean HS BG = 120, mean FBG = 180, BeAM = -60

BeAM in T2D

Adding basal insulin in T2D (N = 1401 and 553)

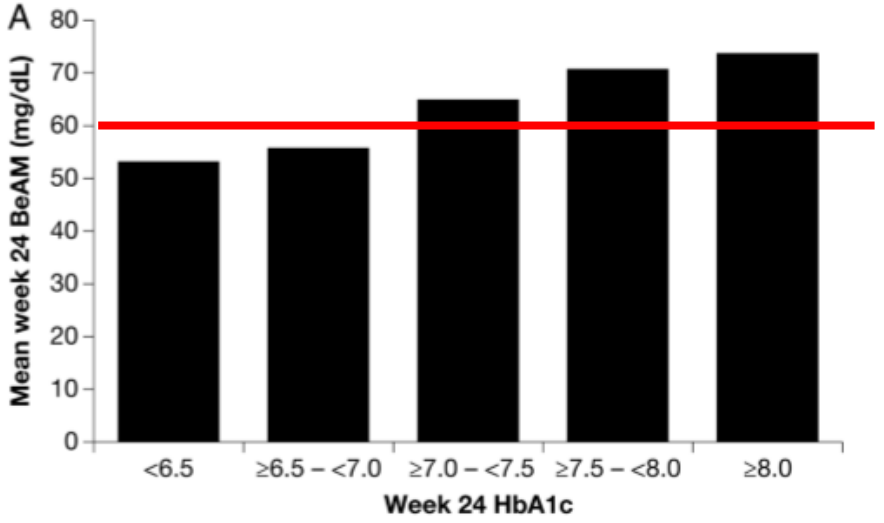


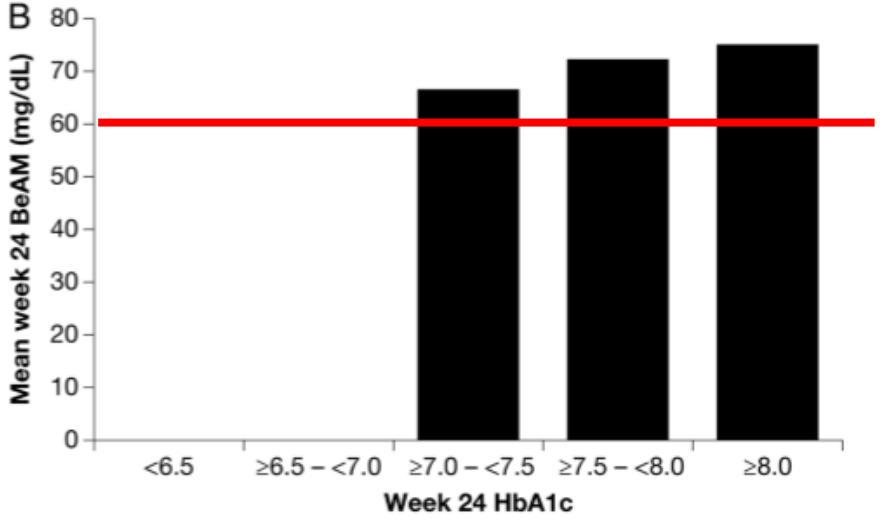
BeAM increased to 60 mg/dL due to lower FBG without change in HS BG

BMJ Open Diabetes Res Care 2016;4:1-8

BeAM in T2D: Basal Insulin Only

In T2D with basal insulin alone, it appears a BeAM level > 60 mg/dL is associated with A1C levels > 7%. Should the goal in T2D on basal insulin be a BeAM < 60 mg/dL?



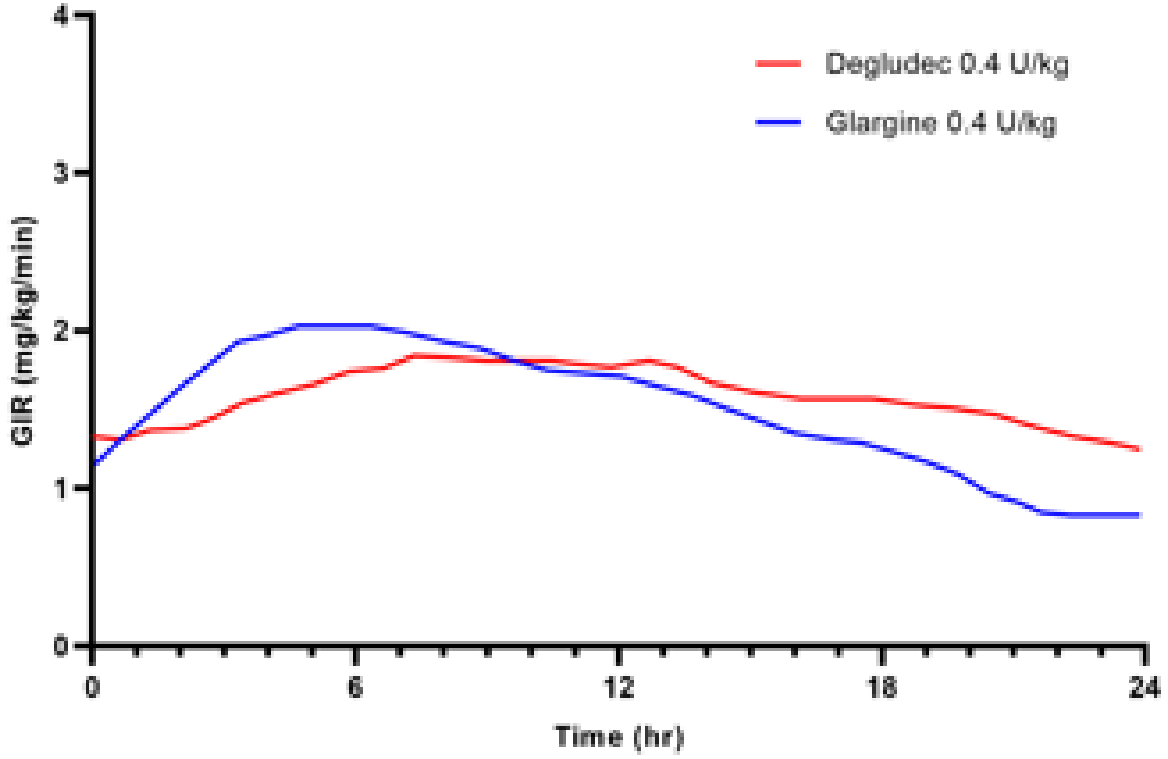


BMJ Open Diabetes Res Care 2016;4:1-8

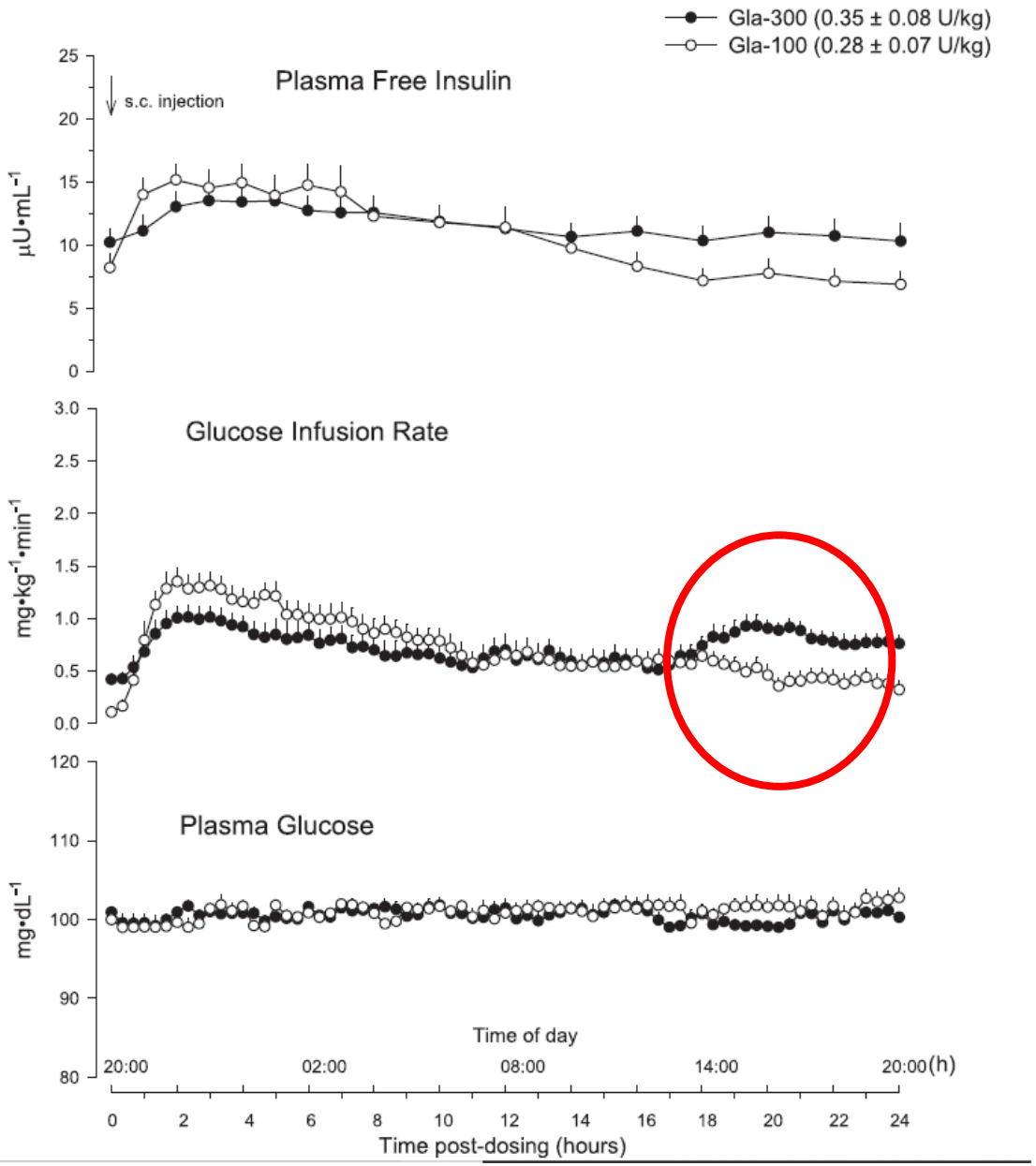
Basal Insulins

- Not all the same!
- NPH-occasionally used for severe dawn phenomenon in T1D, morning steroids, more nocturnal hypoglycemia compared to analogues in both T1D and T2D
- Glargine (U-100): most commonly used basal insulin
- U-300 glargine
- Degludec

Insulin Action Curves: Degludec vs. Glargine



What About U100 Glargine vs. U300 Glargine?



U300 lasts longer than U100 BUT requires about 15% more in the dose

Diabetes Care 2019; 42(1): 85-92.

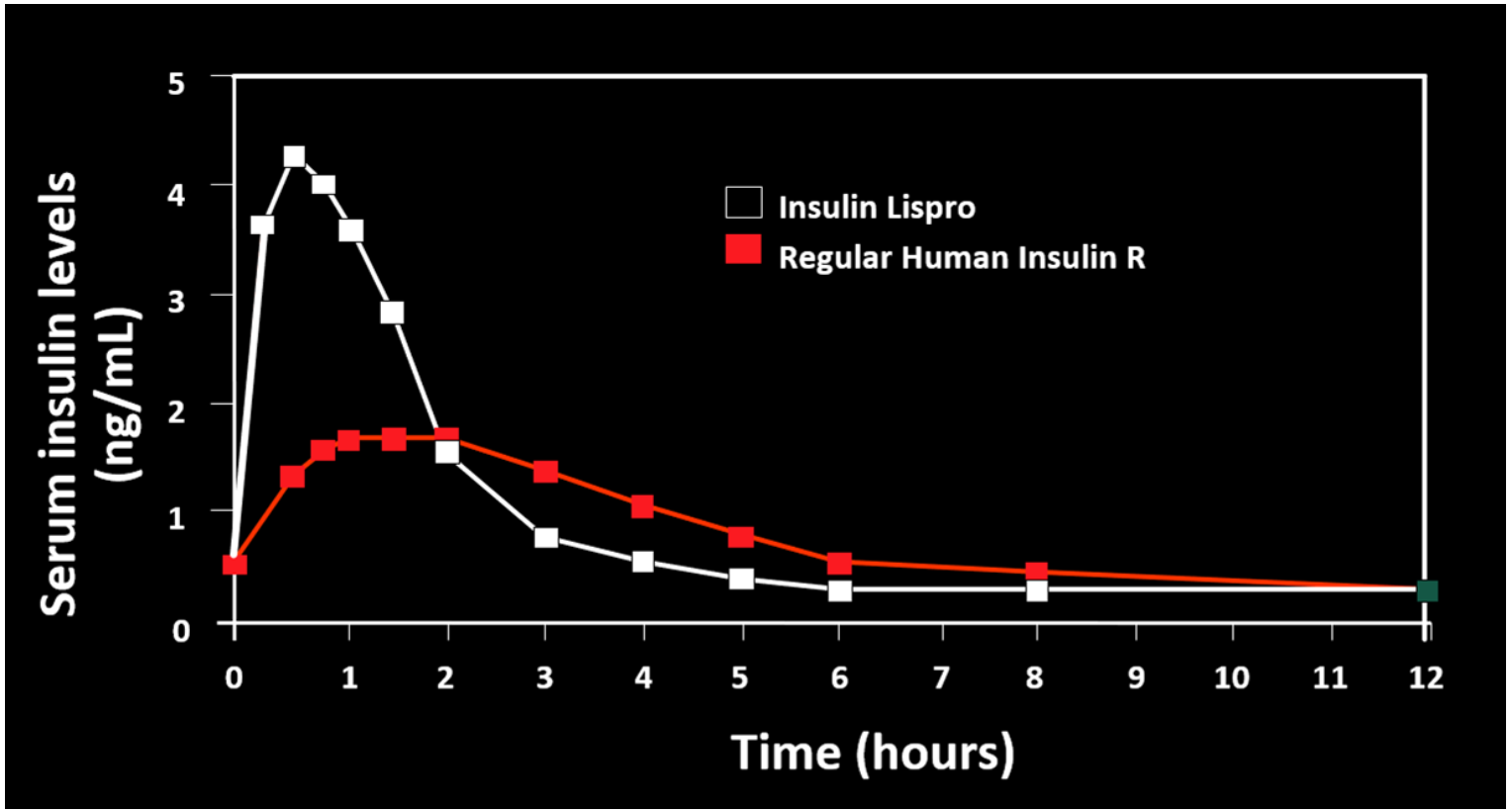
U-100 Glargine vs. Degludec/U-300 Glargine

- Degludec: consistently less hypoglycemia
- U300 glargine: some but not all studies with less hypoglycemia
- Bottom line: Degludec and U300 glargine are better basal insulins than U100 glargine; as a rule of thumb if you can get them, you should (especially for T1D)

Understanding Prandial Vs. Basal Insulin

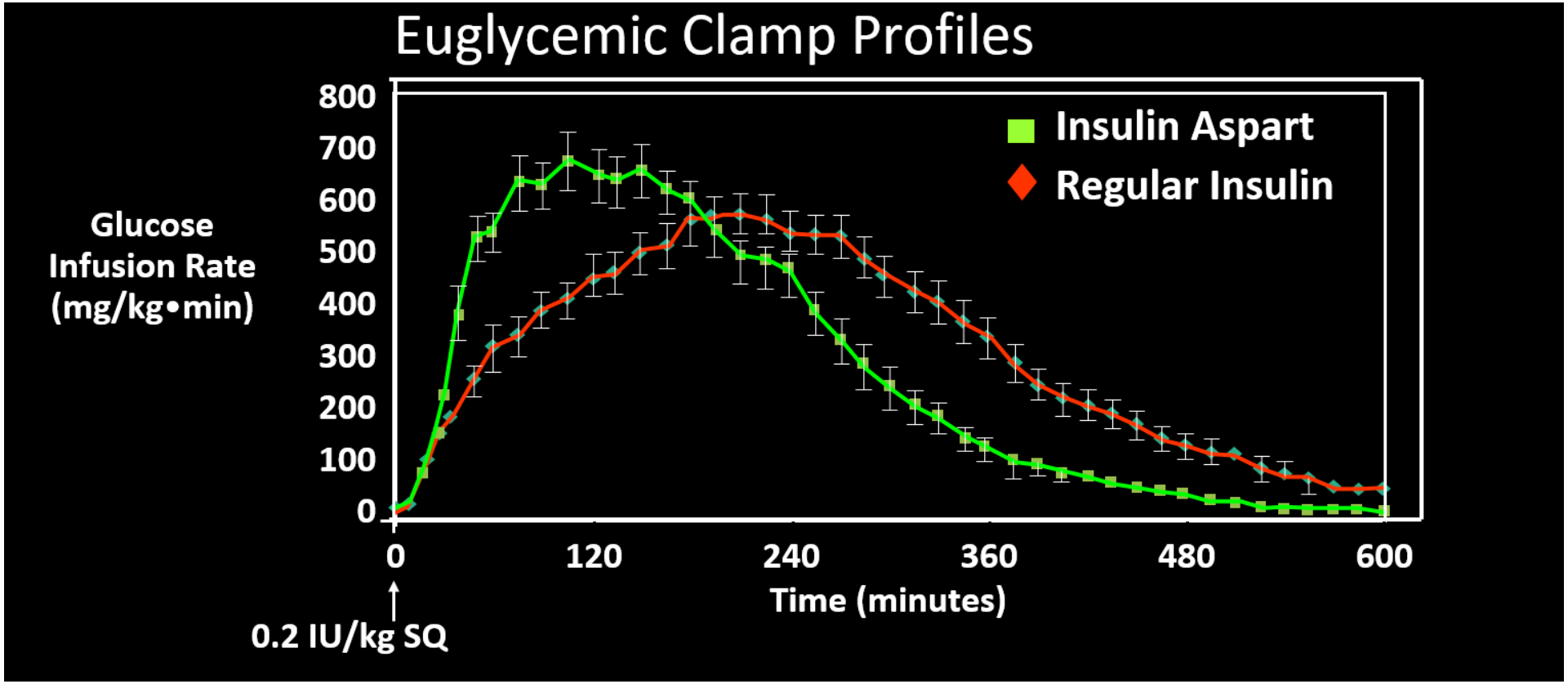
- Prandial insulin
  - Postprandially, 30% taken up by liver, the rest by skeletal muscle

Understand PK vs. PD (lispro)



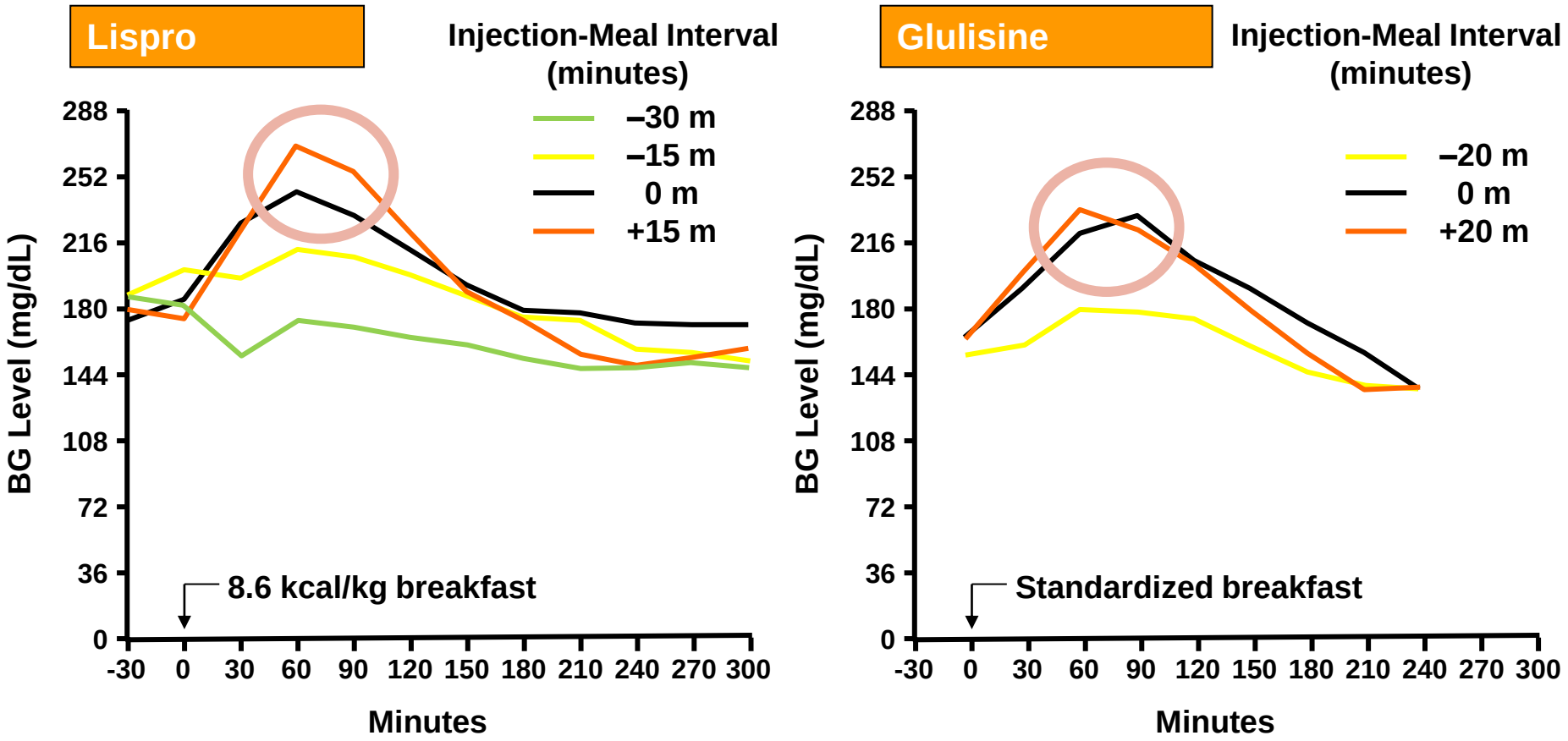
Diabetes 43: 396-402, 1994

Glucodynamic Principles (Analogue Pearl): Prandial Insulin: Not as Rapid Acting as We Thought



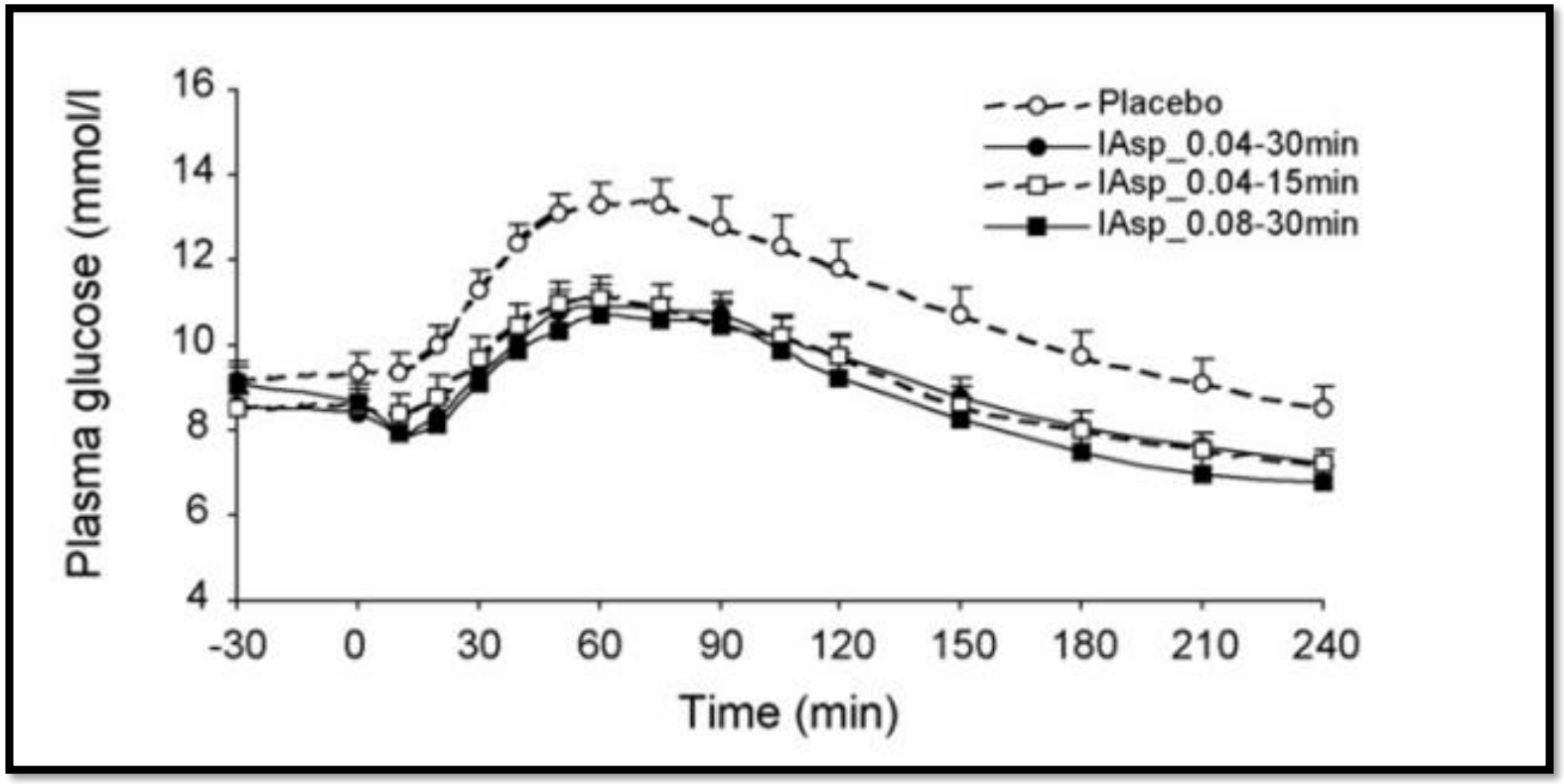
Diabetes Care 1999;22:1501-1506

PEARL 1: Timing (lag time) of Rapid-Acting Analog Insulin Injection Alters PPG in Type 1 Diabetes Mellitus



Diabetes Care 1999; 22:133-136
Diabetes Technol Ther 2010; 12: 173-177

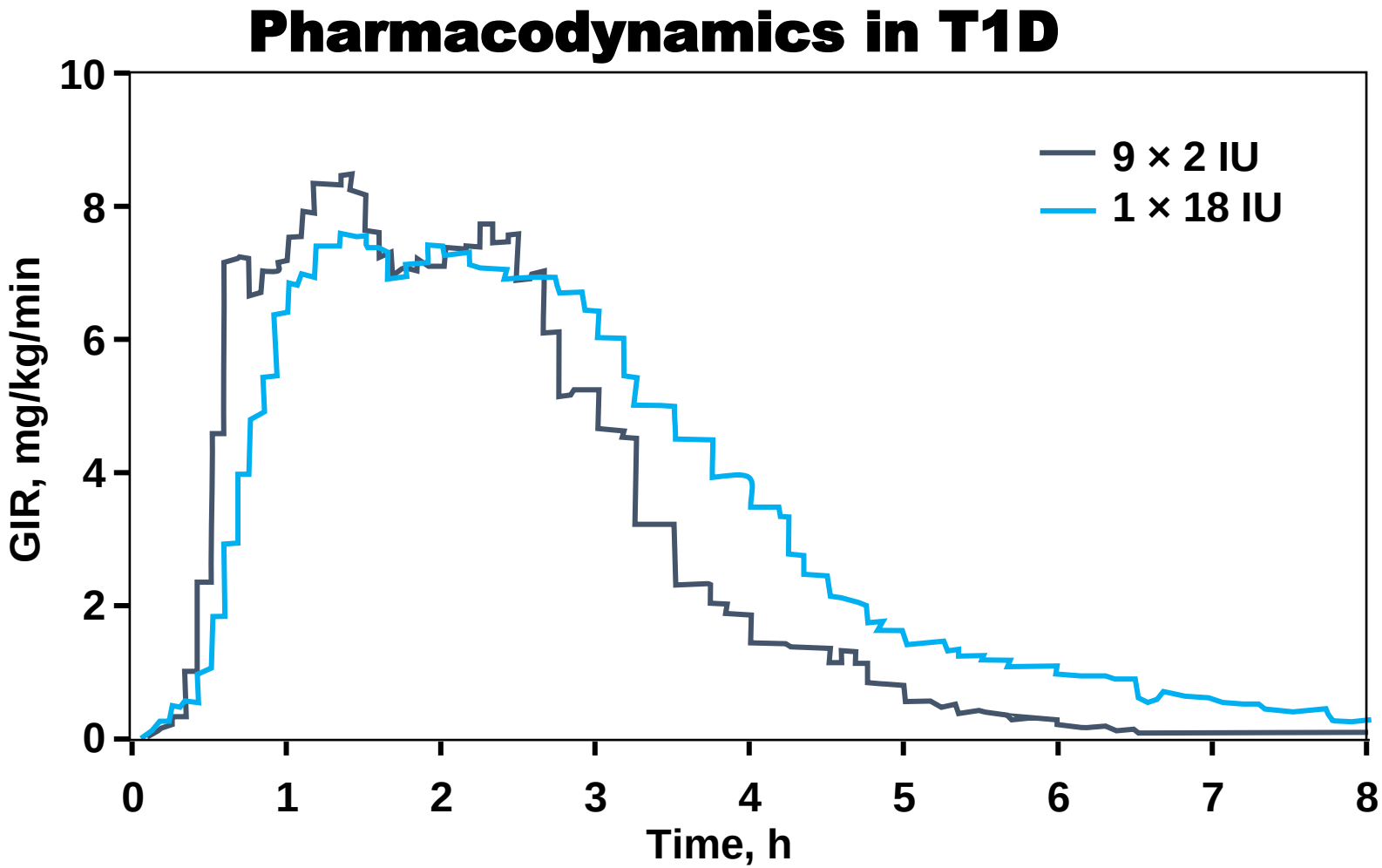
Pearl 1a: Lag Times Do Not Appear as Important in T2D as in T1D



Diabetes Research Clinical Practice 2008;80:293-298

Pearl 2: What About Giving Many Small Doses Instead of One Large Depot (Analogue Pearl)?

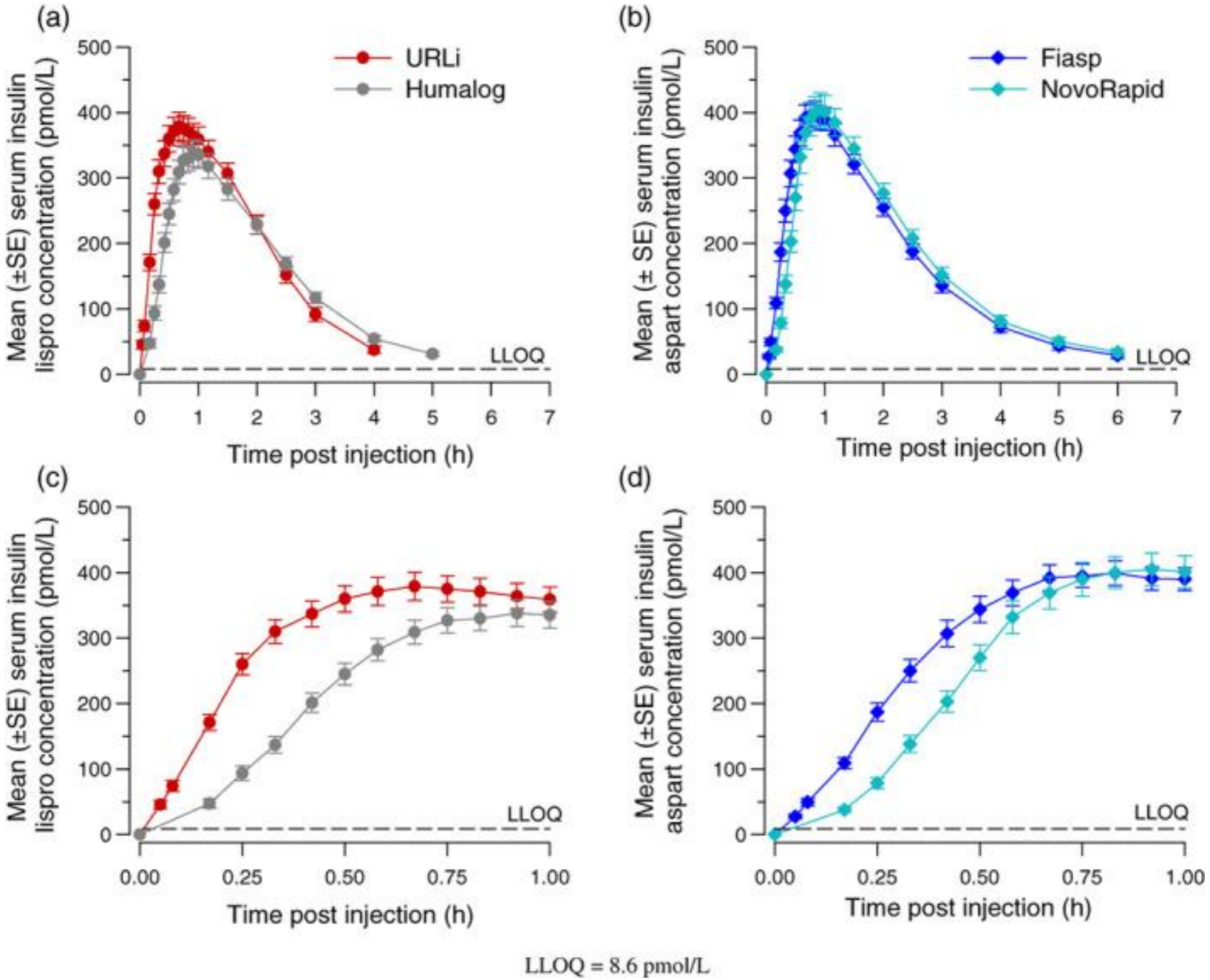
Insulin Aspart PK/PD: Dispersed Injection vs Single Injection
AP@home Consortium



Clamp study of 12 patients with T1D.

Mader JK, et al. Diabetes Care. 2013;36:780-785

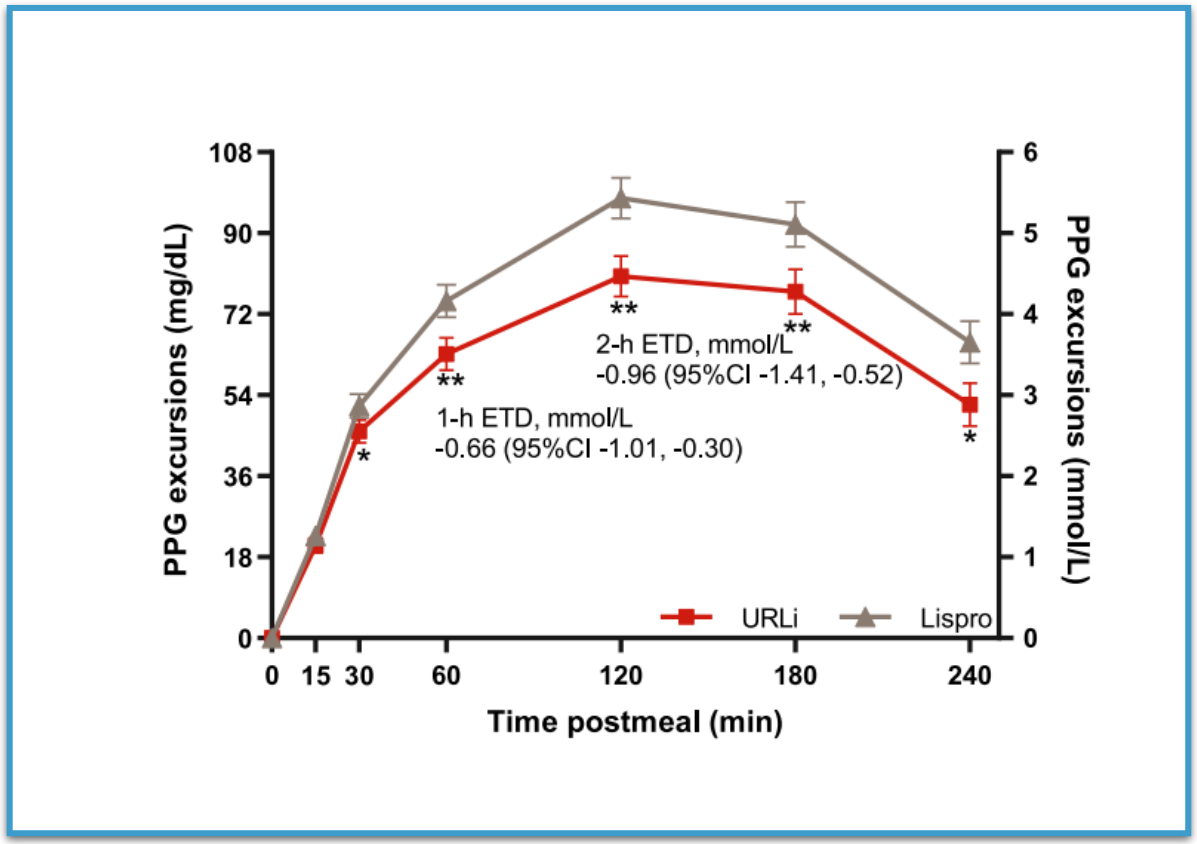
PK URLi, lispro, aspart, fast-acting aspart

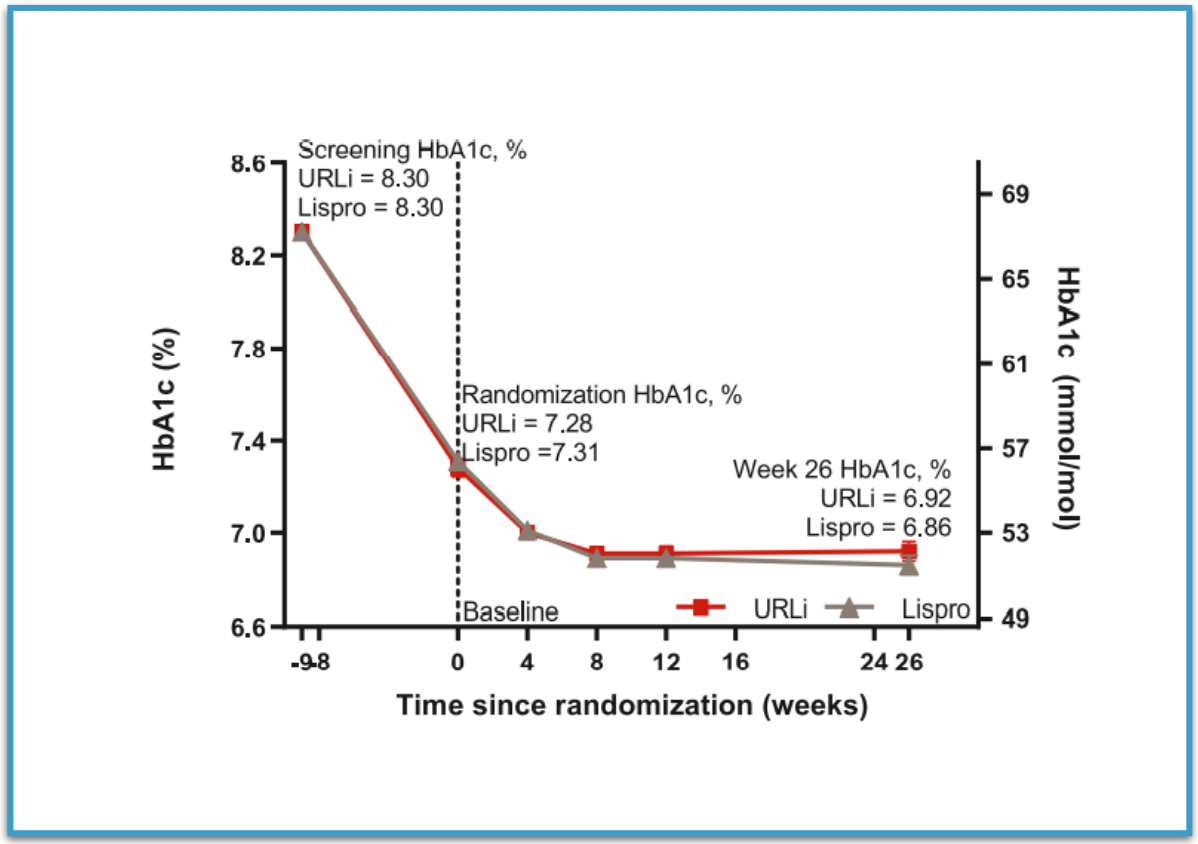


Diabetes Obes Metab. 2020;22:1789–1798

Lispro-aabc in T2D: PRONTO-T2D

N=673





Diabetes Care 2020;43:2991–2998

What is Another Tool to Reduce the After-Meal Spike?

- Post-meal exercise: reduces after-meal spike
- Pre-meal exercise: reduces BOTH pre-meal and post-meal glucose levels

Conclusions

- GLP1-RAs have been a tremendous benefit to people with diabetes due to their ability to lower glucose and weight in addition to CVD and probable renal benefits
- Although expensive (very), the cost of these agents to those with insurance have not increased
- GI side effects are usually but not always manageable.
- Fixed-ratio GLP1-RAs with basal insulin is an important tool to remember

Conclusions

- There are many choices of basal insulin, all with slight differences, but these agents should be started sooner than they currently are with very high HbA1c levels
- BeAM scores are an excellent tool to assess basal insulin dosing
- Prandial insulin choices have increased
- Patients need to learn about the various “pearls” on how to best use these insulins
- In type 2 diabetes, dosing of prandial insulins does not need to be complex (compared to type 1 diabetes) and fixed doses with or without corrections often works well.

THANK YOU

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Patient Case – Advanced Glycemic Management

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Patient Case - Introduction

You are seeing a new patient, a 54-year-old woman with 5 years of T2D who has not seen a physician in 2 years before the pandemic. She takes metformin monotherapy

She has no CVD but takes atorvastatin and lisinopril; her father died from CVD and had an MI at the age of 61 years old. Her BMI is 36.

She has since gained 12 pounds, and on metformin monotherapy her HbA1c has increased from 7.1% to 11.2%.

What is the best option at this time?

A. Add dulaglutide

B. Add long-acting exenatide

C. Add bedtime glargine

D. Add bedtime glargine with mealtime lispro

E. Add the combination of insulin degludec and liraglutide

Patient Case - Continued

- The same patient was started on IDegLira and after 6 months her HbA1c improved from 11.2% to 8.3% at the highest dose (50 units degludec, 1.8 mg liraglutide). Her BMI now is reduced from 36 to 34.
- Fasting and premeal glucose levels are generally in the low-to-mid-100s, but after eating she is often in the mid-to-high 200s.
- What is the best option now?

  A. mealtime lispro

  B. pioglitazone

  C. dapagliflozin

  D. Change the liraglutide to semaglutide and take the degludec separately

  E. Invest in a pharmaceutical mutual fund

Patient Case - Conclusion

- This same patient wants to start an exercise program of fast walks alternating with swimming. What is the best time of day for her exercise?

  A. In the morning before breakfast

  B. Immediately after dinner when her blood sugars are highest

  C. In the middle of the afternoon

  D. At bedtime